27th Annual NICHD Conference on Maternal-Fetal-Neonatal-Reproductive Medicine

Preparing an NIH Grant

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Dr. Hay has no Conflicts of Interest to disclose.

Why do research in the first place?

- Training is learning how to apply what we already know.

  Direct benefit—improved outcomes

- Research is learning about what we don't know.

  Future benefit—solving problems before they cause trouble

More succinctly put--

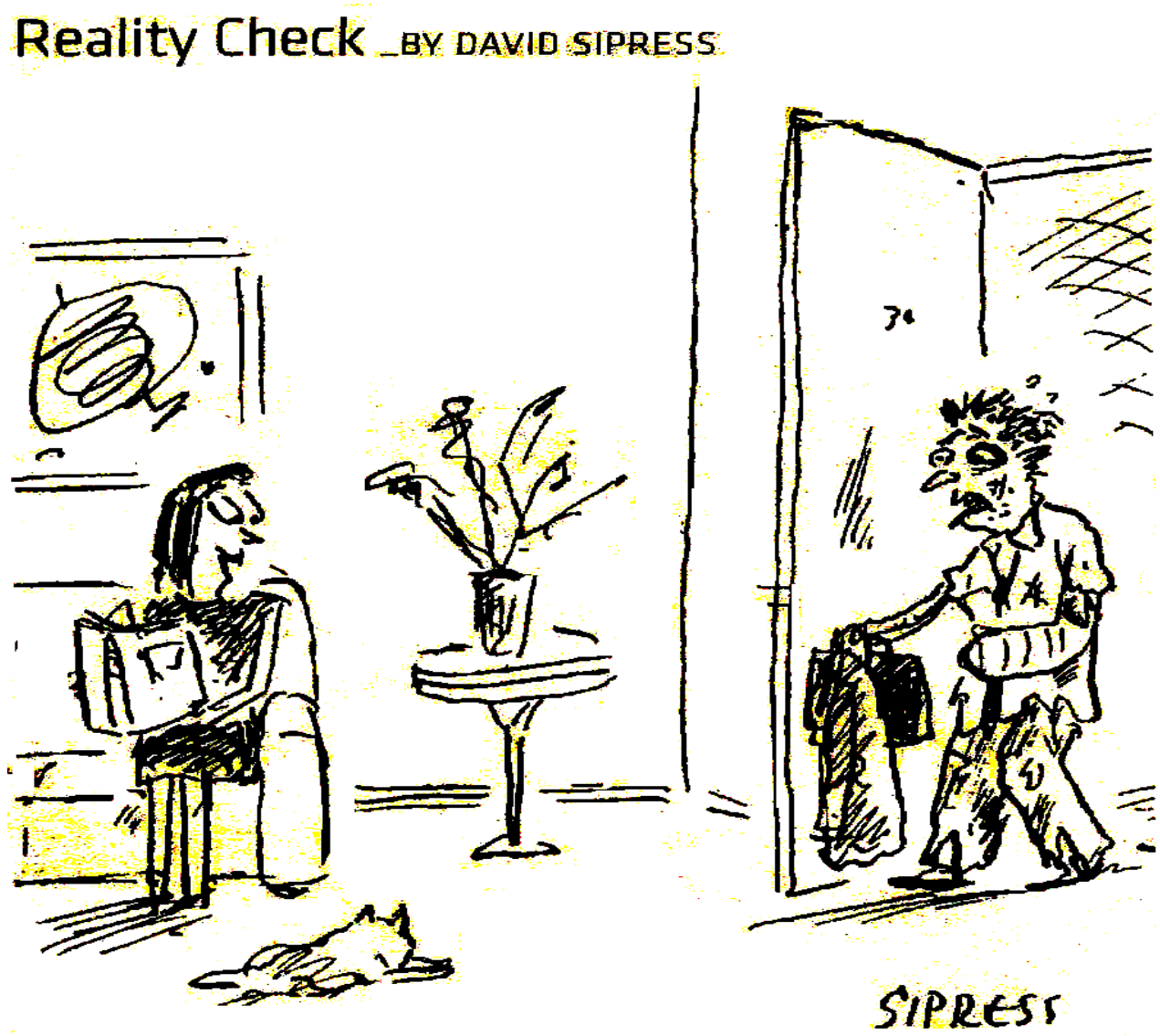
You can see a lot by just looking.

Yogi Berra

First and foremost,
before you do anything about writing grants,
ask yourself if, for you, the most important questions in medicine are about---
How things work?

Is this what excites you?
Is this what drives your curiosity?
Is this what makes you want to get up and go to work every day?

---because in academics this sometimes can be tough to do----



Hi, Honey—how's everything in the world of academia?

Writing a NIH Grant--What to do first!

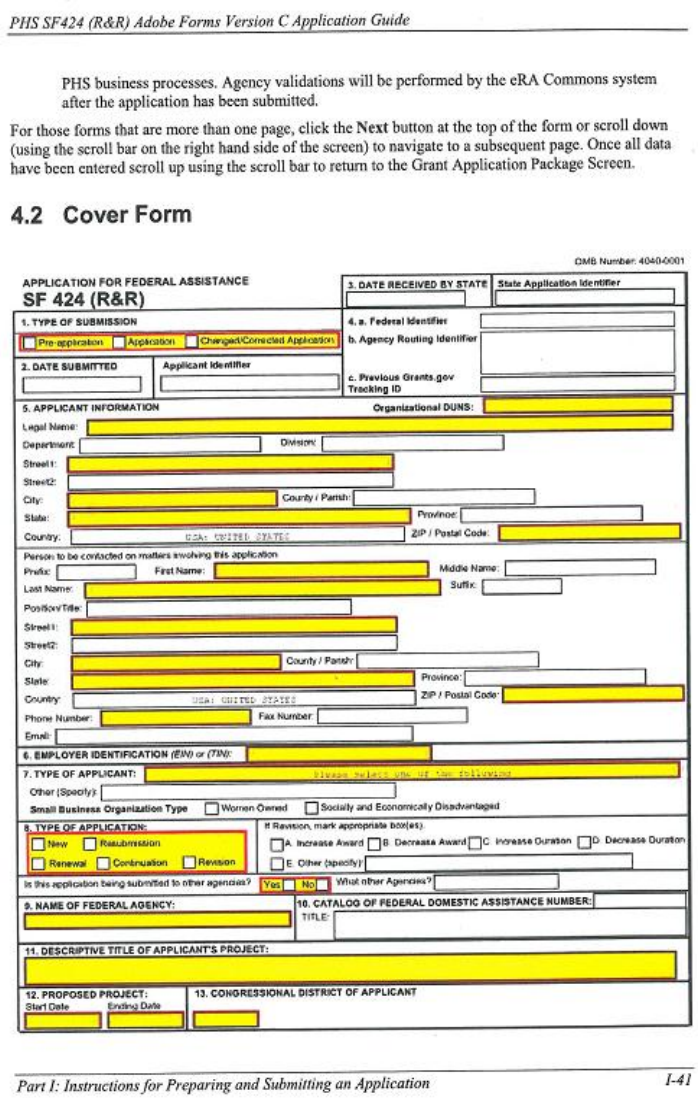
National Institutes of Health website

http://grants.nih.gov.html

Writing a Grant: Start Early!!

- **Receipt Dates:**
  - New (K, R, P, P revision)- 2/1, 6/1, 10/1
  - Revisions (K, R)- 3/1, 7/1, 11/1
  - NRSA (F31-5/1, 11/1; F32- 4/1, 8/1, 12/1; T32- 5/1)
  - SBIR/STTR (R43, R44/R41, R42)- 4/1, 8/1, 12/1
- **Review: 5-6 months later**
- **Council: 3-4 months**
- **Award: 1-2 months**
- **Total time until award: 9-10 months—**
- **Thus, start preparing for a grant application at least a year in advance of when you think you will need the money.**

First, what does an NIH grant application look like?



PHS SF424 (R&R) Adobe Forms Version C Application Guide

PHS business processes. Agency validations will be performed by the eRA Commons system after the application has been submitted.

For those forms that are more than one page, click the **Next** button at the top of the form or scroll down (using the scroll bar on the right hand side of the screen) to navigate to a subsequent page. Once all data have been entered scroll up using the scroll bar to return to the Grant Application Package Screen.

4.2 Cover Form

OMB Number: 4040-0001

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE | State Application Identifier

1. TYPE OF SUBMISSION
Pre-application | Application | Changed/Corrected Application

4. a. Federal Identifier
b. Agency Routing Identifier
c. Previous Grants.gov Tracking ID

2. DATE SUBMITTED | Applicant Identifier

5. APPLICANT INFORMATION | Organizational DUNS:
Legal Name:
Department: | Division:
Street1:
Street2:
City: | County / Parish:
State: | Province:
Country: USA: UNITED STATES | ZIP / Postal Code:

Person to be contacted on matters involving this application
Prefix: | First Name: | Middle Name:
Last Name: | Suffix:
Position/Title:
Street1:
Street2:
City: | County / Parish:
State: | Province:
Country: USA: UNITED STATES | ZIP / Postal Code:
Phone Number: | Fax Number:
Email:

6. EMPLOYER IDENTIFICATION (EIN) or (TIN):

7. TYPE OF APPLICANT: Please select one of the following
Other (Specify):
Small Business Organization Type | Women Owned | Socially and Economically Disadvantaged

8. TYPE OF APPLICATION:
New | Resubmission | Renewal | Continuation | Revision
If Revision, mark appropriate box(es).
A. Increase Award | B. Decrease Award | C. Increase Duration | D. Decrease Duration | E. Other (specify):
Is this application being submitted to other agencies? Yes | No | What other Agencies?

9. NAME OF FEDERAL AGENCY:
10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER: | TITLE:

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT:

12. PROPOSED PROJECT: Start Date | Ending Date
13. CONGRESSIONAL DISTRICT OF APPLICANT

Part I: Instructions for Preparing and Submitting an Application I-41

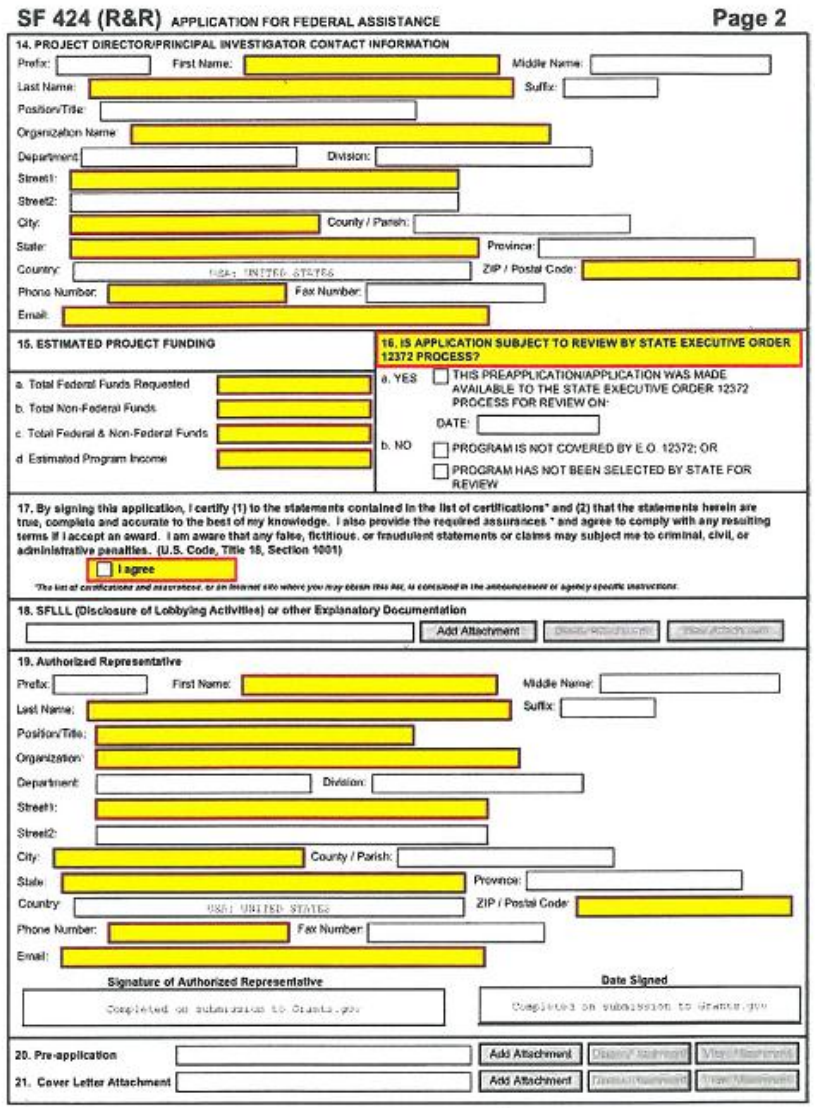
Cover Form

Type of submission

Applicant information

Employer information

Descriptive title of project



SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE — Page 2

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: | First Name: | Middle Name:
Last Name: | Suffix:
Position/Title:
Organization Name:
Department: | Division:
Street1:
Street2:
City: | County / Parish:
State: | Province:
Country: USA: UNITED STATES | ZIP / Postal Code:
Phone Number: | Fax Number:
Email:

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested
b. Total Non-Federal Funds
c. Total Federal & Non-Federal Funds
d. Estimated Program Income

16. IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?

a. YES ☐ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:
DATE:
b. NO ☐ PROGRAM IS NOT COVERED BY E.O. 12372; OR
☐ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

☐ I agree

*The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.

18. SFLLL (Disclosure of Lobbying Activities) or other Explanatory Documentation

Add Attachment

19. Authorized Representative

Prefix: | First Name: | Middle Name:
Last Name: | Suffix:
Position/Title:
Organization:
Department: | Division:
Street1:
Street2:
City: | County / Parish:
State: | Province:
Country: USA: UNITED STATES | ZIP / Postal Code:
Phone Number: | Fax Number:
Email:

Signature of Authorized Representative: Completed on submission to Grants.gov
Date Signed: Completed on submission to Grants.gov

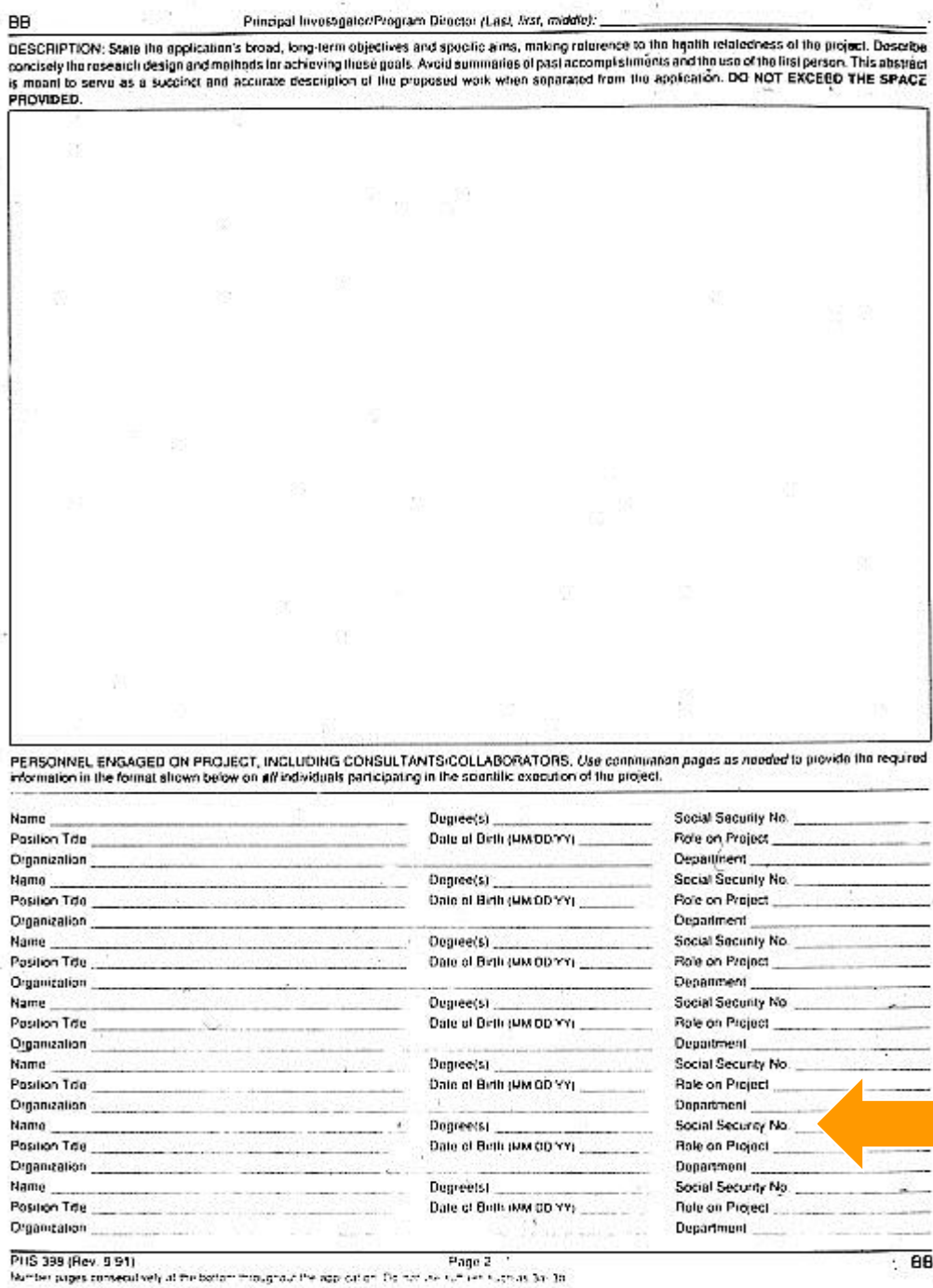
20. Pre-application — Add Attachment
21. Cover Letter Attachment — Add Attachment

Application Page—2

PI name

Estimated project funding

Authorized Institutional official



BB Principal Investigator/Program Director (Last, first, middle):

DESCRIPTION: State the application's broad, long-term objectives and specific aims, making reference to the health relatedness of the project. Describe concisely the research design and methods for achieving these goals. Avoid summaries of past accomplishments and the use of the first person. This abstract is meant to serve as a succinct and accurate description of the proposed work when separated from the application. DO NOT EXCEED THE SPACE PROVIDED.

PERSONNEL ENGAGED ON PROJECT, INCLUDING CONSULTANTS/COLLABORATORS. *Use continuation pages as needed* to provide the required information in the format shown below on *all* individuals participating in the scientific execution of the project.

Name Degree(s) Social Security No.
Position Title Date of Birth (MM/DD/YY) Role on Project
Organization Department
Name Degree(s) Social Security No.
Position Title Date of Birth (MM/DD/YY) Role on Project
Organization Department
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Organization Department

PHS 398 (Rev. 9/91) Page 2 BB

Number pages consecutively at the bottom throughout the application. Do not use suffixes such as 3a, 3b.

The most important page in the application—

Description (Abstract)

WHAT you are going to do, **WHY** you are going to do it, **HOW** you are going to do it, and the **VALUE** of doing it. And always emphasize its **IMPACT**.

Personnel engaged on project

Modular Budget

5.4.1 Budget Period Form

PHS 398 Modular Budget

OMB Number: 0925-0001

Budget Period: 1

Start Date: End Date:

A. Direct Costs

Funds Requested ($)

Direct Cost less Consortium F&A

Consortium F&A

Total Direct Costs

B. Indirect Costs

	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)
1.				
2.				
3.				
4.				

Cognizant Agency (Agency Name, POC Name and Phone Number)

Indirect Cost Rate Agreement Date

Total Indirect Costs

C. Total Direct and Indirect Costs (A + B) Funds Requested ($)

Cumulative Budget Information

1. Total Costs, Entire Project Period

Section A, Total Direct Cost less Consortium F&A for Entire Project Period	$
Section A, Total Consortium F&A for Entire Project Period	$
Section A, Total Direct Costs for Entire Project Period	$
Section B, Total Indirect Costs for Entire Project Period	$
Section C, Total Direct and Indirect Costs (A+B) for Entire Project Period	$

2. Budget Justifications

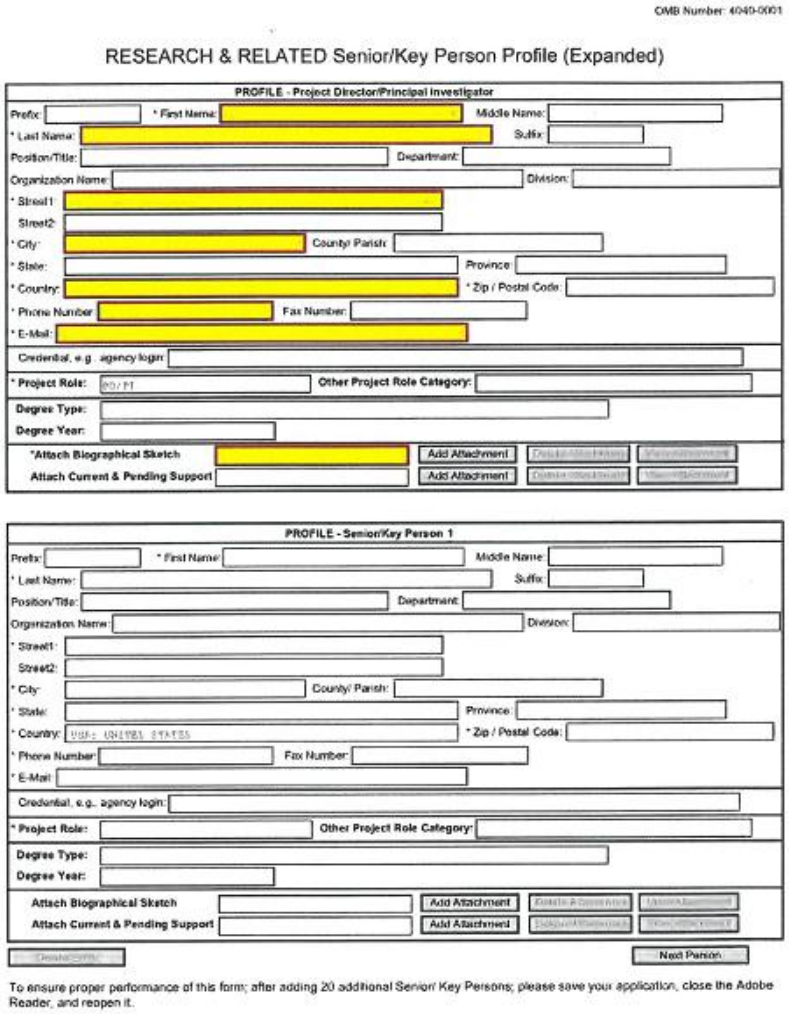
Personnel Justification		Add Attachment
Consortium Justification		Add Attachment
Additional Narrative Justification		Add Attachment

Total Budget Summary

RESEARCH & RELATED BUDGET - Cumulative Budget

		Totals ($)
Section A, Senior/Key Person		
Section B, Other Personnel		
Total Number Other Personnel		
Total Salary, Wages and Fringe Benefits (A+B)		
Section C, Equipment		
Section D, Travel		
1. Domestic		
2. Foreign		
Section E, Participant/Trainee Support Costs		
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other		
6. Number of Participants/Trainees		
Section F, Other Direct Costs		
1. Materials and Supplies		
2. Publication Costs		
3. Consultant Services		
4. ADP/Computer Services		
5. Subawards/Consortium/Contractual Costs		
6. Equipment or Facility Rental/User Fees		
7. Alterations and Renovations		
8. Other 1		
9. Other 2		
10. Other 3		
Section G, Direct Costs (A thru F)		
Section H, Indirect Costs		
Section I, Total Direct and Indirect Costs (G + H)		
Section J, Fee		

4.5 Senior/Key Person Profile (Expanded) Form



OMB Number: 4040-0001

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix: * First Name: Middle Name:
* Last Name: Suffix:
Position/Title: Department:
Organization Name: Division:
* Street1:
Street2:
* City: County/ Parish:
* State: Province:
* Country: * Zip / Postal Code:
* Phone Number: Fax Number:
* E-Mail:
Credential, e.g., agency login:
* Project Role: PD/PI Other Project Role Category:
Degree Type:
Degree Year:
*Attach Biographical Sketch Add Attachment
Attach Current & Pending Support Add Attachment

PROFILE - Senior/Key Person 1

Prefix: * First Name: Middle Name:
* Last Name: Suffix:
Position/Title: Department:
Organization Name: Division:
* Street1:
Street2:
* City: County/ Parish:
* State: Province:
* Country: USA: UNITED STATES * Zip / Postal Code:
* Phone Number: Fax Number:
* E-Mail:
Credential, e.g., agency login:
* Project Role: Other Project Role Category:
Degree Type:
Degree Year:
Attach Biographical Sketch Add Attachment
Attach Current & Pending Support Add Attachment

Next Person

To ensure proper performance of this form, after adding 20 additional Senior/ Key Persons, please save your application, close the Adobe Reader, and reopen it.

Senior Key Person Profiles

FF Principal Investigator/Program Director (Last, first, middle)

BIOGRAPHICAL SKETCH

Give the following information for the key personnel and consultants and collaborators. Begin with the principal investigator/program director. Photocopy this page for each person.

NAME	POSITION TITLE

EDUCATION (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Key personnel include the principal investigator and any other individuals who participate in the scientific development or execution of the project. Key personnel typically will include all individuals with doctoral or other professional degrees, but in some projects will include individuals at the masters or baccalaureate level provided they contribute in a substantive way to the scientific development or execution of the project. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. DO NOT EXCEED TWO PAGES.

Biographical Sketch

OTHER SUPPORT

(Use continuation pages if necessary)

FOLLOW INSTRUCTIONS CAREFULLY. Incomplete, inaccurate, or ambiguous information about OTHER SUPPORT could lead to significant delays in the review and/or possible funding of the application. If there are changes in the information after submission, notify the scientific review administrator of the initial review group before the review; if changes occur after the review, notify the appropriate institute.

Other support is defined as all funds or resources, whether Federal, non-Federal, or institutional, available in the principal investigator/program director (and other key personnel named in the application) in direct support of their research endeavors through research or training grants, cooperative agreements, contracts, fellowships, gifts, prizes, and other means. However, in the case of grants and gifts, only those that support the specific project must be reported. Key personnel are defined as all individuals who participate in the scientific development or execution of the project. Key personnel typically will include all individuals with doctoral or other professional degrees, but in some projects will include individuals at the masters or baccalaureate level provided they contribute in a substantive way to the scientific development or execution of the project.

Reporting requirements are for each of the key personnel, described (1) all currently *active* support and (2) all applications and proposals *pending* review or award, whether related to this application or not. If the support is part of a larger project, identify the principal investigator/program director and provide the data for the relevant subproject(s). If an individual has no active or pending support, check "None." Use continuation pages as needed to provide the required information in the *format* as shown below. Information may be combined as long as the format remains the same. For example, all key personnel who have no other support may be listed on a single page. **DO NOT SEND** in a separate page for each person listed for whom "None" is checked.

Name _____ Active _____ Pending _____ None _____

a. Source and identifying no. _____ P.I. _____

Title _____

b. Your role on project _____ % Effort _____

c. Dates and costs of entire project (For renewals, include only the most recent completed award. List direct and indirect costs separately.)

_____

d. Dates and costs of current year _____

e. Specific aims of project _____

_____

_____

_____

_____

_____

f. Describe scientific and budgetary overlap

g. Describe arrangements you will make if the present application is funded (budget % effort, aims, etc.)

Other Support

Subsequent pages are blank. Fill them with the "Essentials for Grant Proposals"

1. Specific Aims (Hypotheses, Questions, Models: what)
2. Significance (rationale--why)
3. Innovation (what is novel in design, in methods, but especially in what will be learned)
4. Convincing preliminary data (can it be done and well?)
5. Methods, statistical design, potential problems and alternative strategies (the details of how).
6. Expertise of the Investigator (s) (can you do it?)
7. Environment (unique advantages of where you are)
7. Summary, restating long term value (goal) and impact.

Writing a Grant: Getting Started

The absolute requirement for a grant is a good idea.
But do make sure it is about something new.

Hi Daddy, We were talking at dinner tonight about what grandparents do for their jobs. I told Clara (5 yrs old) that you do science experiments to find out how the food gets to babies growing inside their mommies' tummies. Clara looked at me like I was an idiot and said in tones of ringing disgust: "The mommy eats the food and it goes into the baby through the belly button thing." Then she walked off. Sorry, Dad. Guess you need to find a new field of research. Clara already knows all about yours.
Love, Emily

Specific Aims

A one page statement of

what is essential in the proposed research, to:

- **generate interest – many say this is the real key, the "hook" that grabs the reviewers attention and generates real excitement.**
- **demonstrate importance, value — the WHY.**
- **give a concise overview of the research (what will be done, and how this is novel)**
- **clearly state the exceptionally strong IMPACT of your defined, expected results.**

Specific Aims

1. More than two or three Specific Aims usually are too many.
2. Each Aim should be stated in one simple sentence, saying as directly as possible what will be done.
3. Each Aim either should be, or include, a hypothesis to be tested, a question to be answered, a model to be tested for predictability, create a novel design, solve a specific problem, challenge an existing paradigm or clinical practice, address a critical barrier to progress in the field, develop new technology.
4. Each Aim should include a *brief* statement of the purpose, rationale (significance, innovation), and approach.
5. Each aim should have a specific statement of what you expect to learn, and how this will be important.
6. Conclude with a summary statement that emphasizes what you will learn and the **impact** this will have on the field.

SPECIFIC AIMS

Restoration of skeletal muscle growth in the fetus with intrauterine growth restriction (IUGR) is a fundamental priority, as impaired muscle growth is a major contributor to lifelong reductions in muscle mass and metabolic disease risk. There are gaps in knowledge, however, about the basic mechanisms that regulate fetal muscle mass and when in gestation muscle growth is plastic and will respond to anabolic stimuli after exposure to placental insufficiency (PI). Our overarching aim is to determine the mechanisms that link low fetal nutrient supply to decreased muscle growth, and to test, for the first time, whether supplemental nutrients and/or anabolic hormones could restore muscle growth in the IUGR fetus. Our previous studies and preliminary data have uniquely shown that inadequate maternofetal nutrient flow from PI results in suppressed myoblast proliferation, reduced muscle amino acid (AA) uptake, and increased protein breakdown, which, together with reduced fetal insulin and AA availability, decrease muscle mass (Fig 1). We now propose to test the plasticity of these conditions and determine mechanisms that underlie the potential for 1) insulin to stimulate myoblast proliferation and 2) AA to stimulate myofiber hypertrophy during critical developmental windows of myogenesis (Fig 1). We will use our well-developed sheep model of IUGR that uniquely mimics the features of human PI-induced IUGR to determine muscle-specific metabolism in response to insulin and AA. Comprehensive investigation into the key factors that regulate fetal muscle growth at a physiological, cellular, and molecular level is a prerequisite for designing novel approaches to restore muscle growth, setting the stage for future efforts to preempt the complications of IUGR related to low muscle mass.

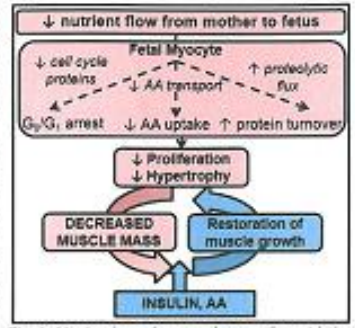


Fig 1. Mechanisms for muscle growth restriction (pink) and interventions to restore growth (blue).

Aim 1: Determine the effect of insulin on cell cycle and proliferative responses in fetal myoblasts. Identifying the primary factors that stimulate myoblast proliferation in IUGR will pave the way for the development of novel strategies to promote myogenesis and preempt the risk of lifelong sarcopenia.

Hypothesis 1a. Correcting insulin concentrations in IUGR fetal sheep increases myoblast proliferation. Fetal insulin concentrations will be restored to control (CON) fetal values by direct fetal infusion during peak myoblast proliferation (70% of gestation). Proliferating myonuclei will be identified using BrdU and PCNA.

Hypothesis 1b. Insulin promotes fetal myoblast proliferation by releasing cells from G_0/G_1 arrest. The impact of insulin on cellular mechanisms that increase cell cycle progression, myoblast proliferation rates, and cell size will be determined in muscle sections and myoblasts isolated from IUGR fetuses.

Aim 2: Establish the impact of AA on fetal myofiber hypertrophy. Identifying the adaptations that develop within the myofiber to chronically-reduced AA supply, and the response to reintroduction of AA, will inform future attempts at how to deliver protein to augment muscle protein accretion.

Hypothesis 2a. AA supplementation to IUGR fetal sheep increases myofiber AA uptake and hypertrophy. Fetal muscle AA kinetics (including muscle protein synthesis and breakdown rates) and myofiber area will be measured in response to fetal AA infusion during peak myofiber hypertrophy (90% of gestation).

Hypothesis 2b. AA promote net protein accretion by increasing AA transport capacity and suppressing protein breakdown in isolated muscles. The impact of AA on cellular mechanisms that regulate hypertrophy will be determined in freshly isolated myofiber preparations and myotubes harvested from IUGR fetal sheep.

Aim 3: Determine the effect of restoring insulin and AA supply on muscle growth in the IUGR fetus. This aim represents a proof-of-concept study of the potential to improve fetal muscle growth, providing an important foundation for the development of novel intervention strategies in IUGR. We hypothesize that sequential fetal insulin and AA infusions during critical developmental windows will increase muscle mass.

Our studies will, for the first time, determine 1) the key regulators that promote fetal myoblast proliferation and myofiber hypertrophy and 2) the critical periods during an IUGR gestation when fetal muscle growth might be recovered. IUGR is a highly prevalent disorder affecting ~8% of all pregnancies, with no known cure and no current means of improving fetal growth *in utero*. Understanding the mechanisms responsible for reduced fetal muscle growth is the first step in preventing low muscle mass, not only for the fetus affected by IUGR, but for other conditions and disorders later in life that result from poor muscle growth.

Specific Aims page

Summary diagram of central concepts helps !

Clearly set off each SA with its overall goal, value, hypothesis, method(s), and what will be learned.

Make sure your summary stands out separately (unlike this one!).

Observation, Hypothesis, Question, Model— what should you use?

Study Sections prefer Inductive Reasoning.

They want you to have some preliminary data and a review of the literature to provide a rationale for what you want to do. They do not want to fund you to "go looking" (observe, characterize, describe, and so forth).

"From this preliminary data in our lab and information in the literature, we—
1. will test the following hypothesis (is it not true <5% of the time?; is it true >95% of the time?);
2. answer the following question (how does something work?);
3. prove the generalizability of this model (predicts that the same mechanism or model will behave in the same way in the future).

Research Strategy (Background, Rationale)

- Not just a literature review (although this must be included).
- Provides the rationale for what you propose to do.

Significance

- Puts your proposed research in perspective---what it will do and the importance of the results.
- How, if the aims of the application are achieved, scientific knowledge will be advanced.
- What the effect of these studies will be on the concepts or methods that drive this field.

Innovation

- How the project develops and employs novel concepts, approaches, or methods.
- How the project challenges existing paradigms—”goes boldly where no one has gone before” (but should).

Preliminary Data

Demonstrates feasibility. Can it be done? Can you do it? Will the results be accurate? Are your methods state-of-the-art? Will the hypotheses probably be supported? Prove that assays and other technical methods in your lab are in working order.

Balance between preliminary data that show

feasibility and likelihood of success

vs.

proof of hypothesis which guarantees success and definitive conclusion

Too much prior proof - no reason to fund, it's done; just filling in "n"

Not enough prior proof - too risky; too unlikely to succeed

Approach (Methods)—5 parts.

1. Experiments

Emphasize the essential experiments.

Refer to literature for established methods.

Identify new methods, their value, and **proof they work.**

2. State clearly what each experiment will demonstrate or prove, **why** that outcome is particularly important to obtain, and what will be the overall **impact** on the scientific field of what you will learn.

3. Potential Problems and Alternative Strategies

Show awareness and thorough understanding of the problems that may arise and the alternative approaches that can be used if the problems occur. State how such variable outcomes actually strengthen the approach.

Approach (Methods)

4. Statistical design and analyses.

How will data be interpreted?

- **This should come early in your grant preparation.**
- **Define the accuracy of your methods.**
- **Then, determine how many animals/subjects are needed for each measurement.**
- **Then, choose the largest number of animals/subjects that will allow a $p<0.01$ test of the least accurate measurement—this allows you more animals/subjects than the most accurate measurement does.**

5. Benchmarks for Success

Define "exactly" what will be learned at each step.

Timeline:
What will be done <u>when</u>

Example 1

NUMBER OF ANIMALS AND TIME TABLE:

Protocol	Year 1	2	3	4	5
1. Developmental changes in placental glucose and amino acid metabolism	20	15			
2. Effect of glucose and amino acid supply on placental amino acid metabolism	5	10	25	25	25
Total # of animals	25	25	25	25	25

Example 2

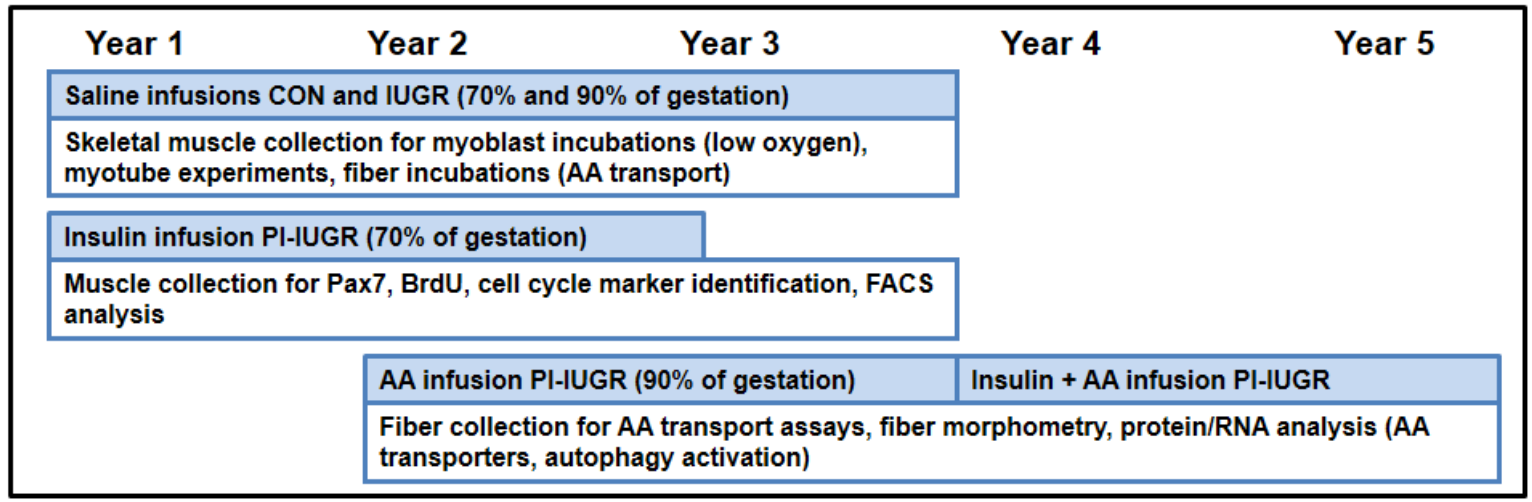


Fig 16. Timeline for in vivo (blue) and in vitro (white) studies.

Summary

What will be learned?

How will the results support the hypotheses (answer the question, test predictability of the model) and meet the specific aims and goals?

How will the results be new and important? IMPACT !

Gaps in our knowledge that this project will fill:

> ***"These studies will determine the fundamental mechanisms responsible for producing cardiorespiratory rhythms that originate in the medulla."***

Why this is not just important but "essential" to do:

> ***"These studies will identify which receptors and processes are altered in diseases of the cardiorespiratory system such as SIDS, allowing novel, specific, more effective therapy, because the current treatments are not working and are unacceptable."***

Animal Care and Use / Human Subjects

Follow the guidelines in the application exactly

Do not assume that your IACUC or IRB protocol is sufficient.

Document that this work has not been done before, that it does require an animal model or a human subject and why, and that all possible non-animal or non-human alternatives have been considered and shown to be insufficient to solve the problem(s) that the research addresses.

Above all, show that all possible discomfort of any kind to the animal or the human subject is known, anticipated, and prevented or minimized

Budget Justification: Prescribed

All Training Grants

T32, F31/32, KO8, K23, K12

-- salary (usually for 75% time)

-- lab support
(usually limited, e.g. $25K)

-- travel (limited, e.g., $1,500)

-- F & A (“Indirects”; limited, e.g., 8%)

Budget Justification: Modular

$25,000/module up to $250,000 (10 modules)

Explain and justify roles of investigators.

Rationale for highly expensive, but essential items.

Budget Justification: Itemized
Direct costs > $250,000

Explain and justify each and every item in the budget.

Personnel: name, degree, title, role--justify by specific expertise and what they exactly will do and why the allotted time is essential.

Equipment: Rationale and evidence for cost and need for expensive, unusual, or absolutely essential items ("convenience" or "efficiency" are not sufficient justifications); show cost-sharing if available.

Supplies: As close to "line item" as possible; provide historical and current use and prices; explain per experiment, pre subject, per animal, per year; charts and tables are helpful; include local special or exceptional requirements.

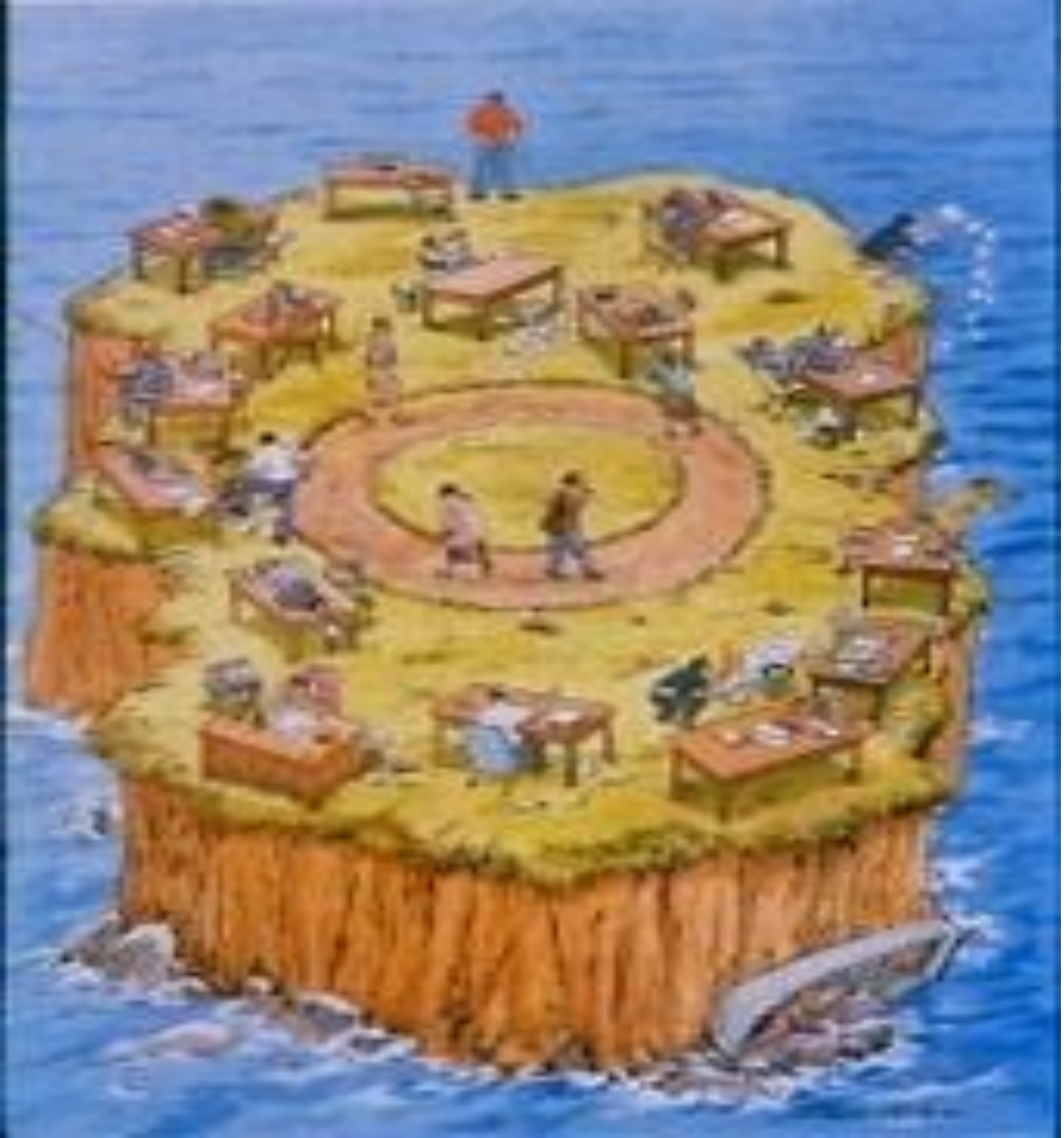
Travel: $1,500 per year for PI is customary, to attend scientific meeting to present results of research

Other: Do not over inflate costs of communications, publications, etc.

Consortium, Contract, and Consultant costs: get these done well ahead of grant due date; the should accomplish a specific task that you clearly show to be essential.

OK, now sit down

and write your application.



What commonly happens at this point is

Writer's Block.

("Block Island")

Even if you are on the right track, you'll get run over if you just sit there.

Will Rogers

"I try to write a little bit every day."

Writing a Grant: General Principles

Start fresh! Don't use grants for templates that were rejected.

Organization: Outline first, write second.

Prepare the figures and tables first. Often these are already done—for abstracts and presentations.

Clarity: Appropriate syntax, clear and lucid style

Short sentences (active voice helps)

Be concise.

Keep it simple! Tell a single story—the more concepts and hypotheses and experiments included, the more difficult to understand.

A golden rule: Never submit a sloppy grant.

Assistance: Have others read it (expert and non-expert).

Key Ingredients

Technical writing:

- Clear statement of need and idea
- Plain language
- White space
- No silly mistakes

Proposal development:

- Explicit link to funder – NIH, Foundation
- Potential impact
- Novelty and innovation

Grand Challenges Explorations
Bill & Melinda Gates Foundation

Clear Statement of Need and Idea

- Why is this idea different?
  - *Do* explain how your solution is innovative and unique
  - *Don't* waste space re-describing the problem
- Provide your project objective and rationale
  - *Do* include how that fits with the topic RFA
  - *Do* state your rationale for success, and define success
  - May have multiple goals and objectives
- Define overarching statement of need in one sentence
- Define your idea to solve this problem in one sentence

Grand Challenges Explorations
Bill & Melinda Gates Foundation

Good Editing—The Most Essential Aspect of Good Writing

Why? Because bad editing preserves bad writing, which leads to misunderstanding, and all too often to confused and therefore sometimes hostile (or stupefied) reviewers.

For example, you do not want these in your grant—

- "…causes of which include, but are not limited to, maternal malnutrition, maternal hypertension, and **idiopathetic** placental insufficiency."
- "These fetuses are at increased risk of hypoglycemia, hypoxia, and **academia**, as well as spontaneous preterm delivery…"

Fortunately, I am not alone in making this mistake--

"…this report underscores the difficulty for obstetricians to identify…babies destined to develop academia,…"

A. Fanaroff MD

2010 Year Book of Neonatal and Perinatal Medicine

And just for fun--

"…pathway to stop diabetes research grants…"

Maybe not the most successful pathway?

Perhaps better as—grants for the "pathway to stop diabetes" program.

"If you don't write clearly, you deserve to be misunderstood."

Words NOT to use

Characterize
Evaluate
Describe
Look at
Check
Estimate
Correlate
Observe
Study
Ask / Question
Compare

Words better to use

Test
Define
Determine
Measure
Quantify
Prove / Disprove

And don't use "alter" or "change"

use "increase" or
or "decrease"—
or "changed from … to …"
Be specific!

Don't use words you don't absolutely need.

"Utilize" is over used (not over utilized).

"Use" is just fine.

(exception—metabolic rates are "utilization" rates)

Direct, active voice.

We measured three cognitive outcomes.

not, Three cognitive outcomes were measured.

Don't run sentences/phrases together with "however"

Confusing-- We found separate effects of glucose and insulin however the insulin effect was the strongest.

Better-- We found separate effects of glucose and insulin; insulin was the strongest.

And many more!

Strunk & White, *The Elements of Style*---still the bible of writing English

Whoops!! —CHECK SPELLING AND GRAMMAR !!

Did you catch my mistake in the previous figure?

Don’t run sentences/phrases together with “however”: Confusing-- We found separate effects of glucose and insulin however the insulin effect was the ~~strongest~~ stronger.

Better-- We found separate effects of glucose and insulin; insulin was the ~~strongest~~ stronger.

Thanks to Alan Guttmacher and Ed Bell for catching this egregious error!!

Good Editing—Get rid of excess words.

Where is the wisdom we have lost in knowledge?

Where is the knowledge we have lost in information?

T. S. Eliot

Good Editing—Over and Over Again

“… everything you do you have to do again, and your capacity for rewriting is the only thing that separates you from people who do things in a hurry.”

John Irving

We are what we repeatedly do;

Excellence, then, is not an act,

But a habit.

Aristotle

Use Plain Language

- Reviewers include deep domain experts and thought leaders (who may not be deep domain experts)

- Write in easy, conversational language
  - *Do* write plainly
  - *Don't* use jargon specific to your field

Grand Challenges Explorations
Bill & Melinda Gates Foundation

Use Plain Language

Passive vs. active voice

- *Passive:*

Research has been cited to demonstrate that an estimated 20% of primary school children are developing reading problems

- *Active*

Researchers estimate that up to 20% of primary school children have reading problems.

Write it plainly

- *Verbose:*

“Scintillate, scintillate, diminutive celestial body”

- *Written plainly:*

“Twinkle, twinkle, little star”

Active voice and plain writing

→ Provide clarity

→ Save space

Grand Challenges Explorations
Bill & Melinda Gates Foundation

Make the Application look good.

“Appearance is everything”

“Clothes maketh the man (or woman).”

Not quite true, but never, ever underestimate the **“power of presentation”**

Bad research page, difficult to read, poorly organized.

water content to hematocrit[46]. *Blood ^{14}C-glucose* is measured using ion exchange chromatography according to Hay et al.[47].

Calculations: Umbilical and uterine blood flow rates are calculated using tritiated water (^3H_2O) by the transplacental steady state diffusion technique.[28]

Net uterine or umbilical uptake rates by the fetus from the placenta of amino acids (including leucine), KIC, glucose, and oxygen are determined by application of the Fick principle:

Uterine or umbilical uptake rate = Uterine or umbilical blood flow (mL/min) x (C_v-C_a) or (C_A-C_v) where C_A and C_v, and C_v and C_a, are the concentrations (□mol/mL) of the metabolite measured in the Uterine arterial and venous, or umbilical venous and fetal arterial blood, respectively. Similarly, net fluxes of ^{14}C-leucine, ^{13}C-leucine, and ^{13}C-KIC across the umbilical (or Uterine) circulation are measured by the Fick principle as umbilical (or uterine) blood flow times the umbilical (or Uterine) tracer arteriovenous concentration difference.

Tracer fluxes: Maternal plasma leucine disposal rate (DR_M) is calculated as:

DR_M = Inf • ([MPE $_{inf}$/MPE$_A$]-1)

where Inf is the infusion rate of L-[1-^{13}C] leucine into the mother and MPE$_{inf}$ and MPE$_A$ are the leucine enrichments in the maternal infusate and maternal arterial plasma, respectively. This equation does not account for the disposal rate of the naturally occurring ^{13}C-labelled leucine which is about 1.1% of the ^{12}C-leucine.[48,49] This equation assumes 100% enrichment of the infused isotope. Plasma [1-^{13}C leucine] is calculated as the product of the leucine concentration and the molar percent excess for ^{13}C leucine in each vessel.

Tracer fluxes between the placenta and the fetal plasma, and between the fetal plasma and fetal tissues, are calculated according to Carver, et al.,[5] Loy, et al.,[45] and Ross, et al.[43]

The fraction of fetal leucine tracer infusion taken up by the placenta ($^{Leu}\Sigma_{umb}$) is calculated as:

($^{Leu}\Sigma_{umb}$) = ([1-^{14}C leucine]$_{a-v}$ x umbilical blood flow) / [1-^{14}C] leucine infusion rate.

The fraction of L-[1-^{14}C] leucine infusion rate excreted as $^{14}CO_2$ via the umbilical circulation ($^{CO2}\Sigma_{umb}$) is calculated as:

($^{CO2}\Sigma_{umb}$) = ([$^{14}CO_2$]$_{a-v}$ x umbilical blood flow)/ [1-^{14}C] leucine infusion rate

The net $^{14}CO_2$ flux from the fetus to the placenta is calculated as:

r$^{14}CO_{2,f}$ dpm/min = umbilical blood flow • ([$^{14}CO_2$]$_a$ - [$^{14}CO_2$]$_v$)

where [$^{14}CO_2$]$_a$ and [$^{14}CO_2$]$_v$ are the concentrations of $^{14}CO_2$ (dpm/mL) in the umbilical arterial and venous blood, respectively.

Tracer model: The model (Carver, et al., Appen. II, Pub. Man. 8) is adapted from Loy, at al.,[45] van Veen, et al.,[34] and Ross, et al.[43] In steady state, the fetal plasma leucine pool is constant in amount, balanced by equal rates of entry (from placenta and fetal tissues) and disposal (into placenta and into fetal tissues). These fluxes of leucine into and out of the fetal plasma, fetal tissues, and the placenta, which apply to the two tracers as well, are shown in the figures below; each flux is labelled with a Roman numeral after Carver, et al.[5]

water content to hematocrit[46]. *Blood ^{14}C-glucose* is measured using ion exchange chromatography according to Hay et al.[47].

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The net $^{14}CO_2$ flux from the fetus to the placenta is calculated as:

r$^{14}CO_{2Af}$ dpm/min = umbilical blood flow • ([$^{14}CO_2$]$_a$ - [$^{14}CO_2$]$_v$)

where [$^{14}CO_2$]$_a$ and [$^{14}CO_2$]$_v$ are the concentrations of $^{14}CO_2$ (dpm/mL) in the umbilical arterial and venous blood, respectively.

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A Bad Research Plan Page

Too much text; outline and separate sections not clearly set off

uptake and utilization, [redacted] glucose, fetal hypoinsulinemia, and decreased placental and fetal growth (Appen. Pub. 3).

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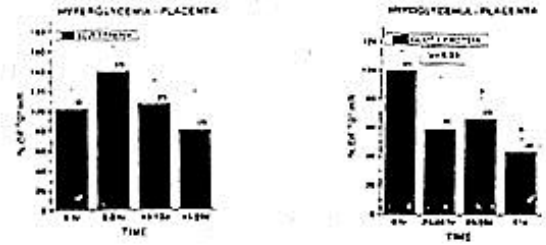
6. Maternal glucose tracer metabolism by the placenta: We conducted the first ever studies of the fate of maternal glucose carbon, traced with [U-^{14}C]glucose infused into the maternal circulation, taken up and metabolized by the placenta and/or transported to the fetus. As shown in the figures below, the fraction of glucose ^{14}C showing up on amino acids was small and was not affected by short or long-term hyperglycemia, whereas chronic hyperglycemia increased the fraction of glucose carbon that was converted to CO_2, both in the fetus and in the placenta.

7. Placental metabolism: We also measured with [U-^{14}C]glucose net uteroplacental glucose consumption rate (UPGC), lactate and fructose production rates, and glucose oxidation in late gestation pregnant sheep after 18 hours each of low and high maternal and fetal glucose concentrations. **A major fraction of UPGC went to non-oxidative metabolism; UP oxygen consumption was not affected; UP lactate production was a major product of UPGC (69% during low glucose, 53% during high glucose);** UP fructose production was 5% under low and 3% under high glucose, and tracer-derived umbilical vein lactate uptake from the placenta was accounted for completely by net fetal lactate uptake from the placenta, i.e., there was no substrate source of UP lactate production into the fetus other than UPGC (Appen. Abst. 4).

8. Maternal low protein diet: Although we have had considerable experience manipulating maternal diet (fasted states, several week periods of glucose and insulin clamps), for the specific purpose of developing a low protein diet in the mother that will lead to reductions in maternal amino acid concentrations, we have engaged the assistance of Dr. Alan Bell (Cornell Univ.), an expert in maternal and fetal effects of maternal dietary changes who has developed and studied maternal low protein diets in pregnant sheep that have produced fetal growth restriction (Appendix IV). Dr. Bell will help to determine the necessary diet formulation to produce an energy complete, low protein diet (see Methods).

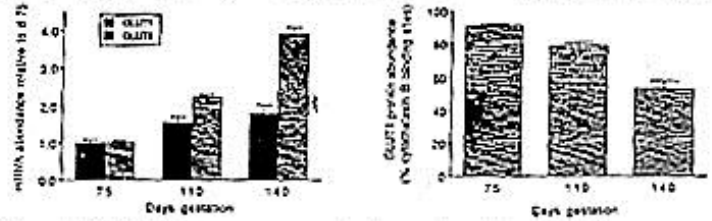
9. Leucine infusion into normal and growth restricted fetuses or their mothers. Leucine infusion into ewes with placental insufficiency showed markedly increased uterine leucine uptake but only slight increase in fetal leucine uptake. Leucine infusion into normal fetuses produced increased leucine oxidation (accounting for increased disposal) and decreased umbilical leucine uptake. Other amino acids were affected by this infusion. Thus, although the placenta actively transports amino acids from the maternal to the fetal circulation, such transport can be affected by the relative maternal and fetal amino acid concentrations.

Another Bad Page
Figures and table too small to see



CONTINUATION PAGE: STAY WITHIN MARGINS INDICATED

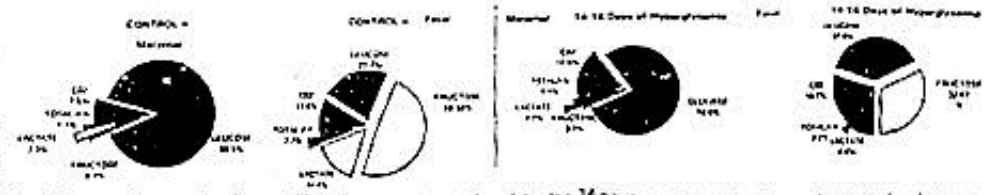
We also have engaged the assistance of Dr. Alan Bell and his doctoral student, Richard Erhardt, to measure GLUT-3 and GLUT-1 mRNA using their ovine-specific cDNA probes. They have nearly completed development of ovine-specific GLUT-3 and GLUT-1 antibodies that will allow us to measure protein abundances for more direct correlation with glucose uptake and transport studies in vivo. Data below show a relative increase in GLUT-3 vs 1 mRNA (left) over the second half of gestation, with a corresponding decrease in the fraction of total cytochlasian binding capacity (representing "functional" protein abundance) accounted for by GLUT-1 (right).



13. Effect of IGF-I infusion on maternal, placental, and fetal insulin, glucose, and amino acid concentrations. Recombinant human IGF-I from Eli Lilly Co. was infused at constant rate (30μg/hour/kg) into 5 near-term pregnant sheep, increasing mat. [IGF-I] 3.2-fold (comparable to Gluckman's study[21]), decreasing mat. [insulin] from 23 to 3 μU/mL, and decreasing mat. [glucose] from 3.7 to 3.2 mM; on balance, maternal glucose turnover, uptake and utilization of glucose by the placenta and fetus, and placental lactate production were not significantly altered. Most maternal amino acid concentrations were decreased (* $p<0.05$ in table below).

14. Statistical methods: We have developed unique statistical methods, including two and three dimensional generalized Michaelis-Menten response surface methods (Hirst et all and curve fitting methods (Young et all, to interpret and develop models from our complex data that involve multiple measurements within an animal, at different times, of different parameters that may or may not have separate and/or joint effects, and among groups with different numbers of subjects (Appendix II, Pub. Man. 6,7). For the first time, these important advances in statistical modelling will be applied to placental metabolism to address the separate and/or joint effects of substrate supply on selected substrate metabolism in the placenta.

A BAD Page
Figures too small to see



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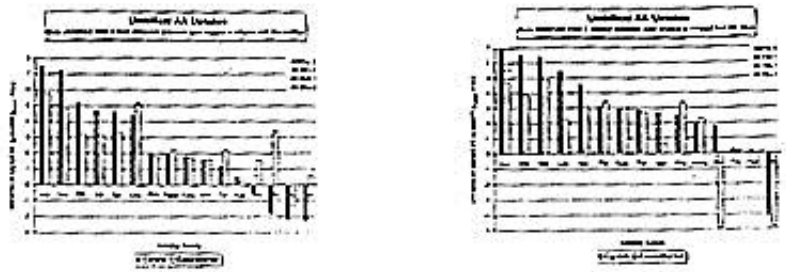

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A "GOOD" Background/Preliminary Data Page

3. Maternal insulin infusion chronic hypoglycemia model: These studies showed that we can maintain maternal glucose concentrations at different levels over several weeks (as well as more acutely [11,41]), by glucose/ insulin clamp technique, to produce sustained decrease in fetal glucose uptake and utilization, an increase in the placental/fetal glucose utilization rate ratio, fetal hypoinsulinemia, and decreased placental and fetal growth (Appen. Pub. 3).

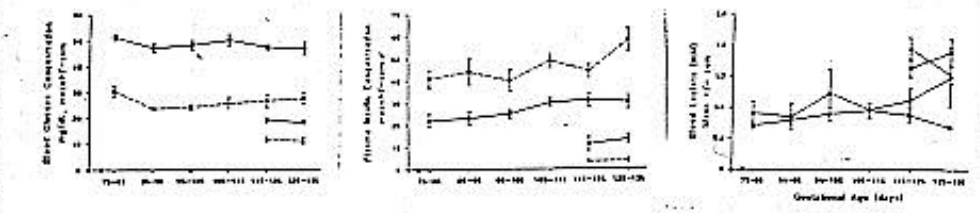

Fig. Stability of maternal and fetal [glucose] and [insulin] over gestation in the maternal hypoglycemia model.

4. Fetal amino acid metabolism: we have published before our methods for measuring maternal and fetal amino acid concentrations and the transfer of amino acids into the fetus (42,43), including details about how to measure fetal amino acid metabolism for several amino acids, and for glucose (11,38,45). These studies have been modified recently for leucine (see details below, in Methods, and Appen., Pub. Man. 8) and for glutamine, and glutamate ( ); more recent pilot studies with arginine are reviewed below.

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Flux rates (mean±sem) (**P<0.01)	Control	Hypoglycemia
[1-^{13}C] leu fetal plasma disposal rate	8.7±0.9	8.2±0.9
[1-^{14}C] leu fetal plasma disposal rate	8.5±0.9	8.4±0.8
net fetal leucine uptake from placenta	4.2±0.6	2.1±0.4**
leucine into blood from fetal proteins	2.0±0.1	3.8±0.3**
CO_2 produced by fetus from leu 1-C	2.1±0.1	1.9±0.3
leucine into fetal protein accretion	2.6±0.2	0.8±0.1**
leucine into fetal protein synthesis	4.6±0.3	4.6±0.2

CONTINUATION PAGE: STAY WITHIN MARGINS INDICATED

Aim 1: Determine the effect of insulin on cell cycle and proliferative responses in fetal myoblasts.

Rationale: Myfiber number is normally set at birth by proliferation and fusion of myoblasts into multinucleated myotubes (69). In a variety of species, maternal nutrient restriction during pregnancy limits fetal myoblast cell cycle activity, reduces myonuclei per myofiber, and reduces myofiber number in offspring (79-88). Factors that regulate myoblast proliferation in the IUGR fetus are not known. Thus, the goals of Aim 1 are to 1) understand the mechanisms whereby reduced fetal nutrient supply limits the number, size, and cell cycle activity of fetal myoblasts, and 2) determine the recoverability of cell cycle activity and myoblast proliferation with restoration of insulin concentrations. An understanding of how the fetal myoblast adapts to low nutrient supply will provide novel and essential knowledge about how myofiber number is determined during fetal life.

Preliminary data: RNA from late gestation CON and IUGR fetal muscle was analyzed by microarray using an Affymetrix® Bovine Gene Chip and 1222 genes were differentially expressed (fold change >1.5 and $P<0.05$). The most significantly impacted gene group was cell cycle regulation. Pathway analysis (89) identified 40-50% reductions in the expression of genes in IUGR muscle that regulate the passage of cells through G_1 to DNA synthesis (S) phase (Cdk4, Cyclin E2, MCM6), G_2 to mitosis (M) (Cyclin B_1, Cdk1, Plk) and spindle assembly (Chk1, Bub1b, Cdc20, Espl1, Mad2). Inhibitors of G_1 to S (p21, Rb-1) were increased by 25% in IUGR muscle.

The pool of Pax7-expressing myoblasts is preserved in IUGR. Given these findings from whole muscle biopsies, we directed our attention to Pax7-positive myoblasts that have the capacity to proliferate and have not terminally differentiated and fused into mature myofibers. We counted Pax7+ myonuclei in CON and IUGR muscle sections harvested at 90% of gestation. Interestingly, we found that the percentage of Pax7+ myonuclei per total nuclei number is preserved in the tibialis anterior (Fig 6a), soleus, and biceps femoris muscles. However, recently published data show that Pax7+ myoblasts in IUGR muscle express less PCNA compared to control, providing evidence for less active proliferation of the myoblast pool (1). Furthermore, our preliminary estimate of total myofiber number in the extensor digitorum longus muscle show fewer myofibers in the IUGR fetus compared to CON (Fig 6b). These data indicate that even though IUGR muscle maintains the pool of myoblasts with proliferative capacity (Pax7+), they have slower proliferation rates, which could contribute to fewer myofibers. Aim 1 will address several questions, including 1) which physiological factors contribute to decreased Pax7+ proliferation, 2) whether size of Pax7+ myoblasts is reduced (e.g. is the population of cells adequate, just smaller in size), and 3) the degree to which restoration of growth factor concentrations in the IUGR fetus increases myoblast proliferation, size, and myofiber number.

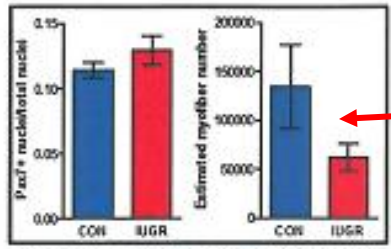


Fig 6. Pax7+ myonuclei in tibialis anterior muscle (n=7/group). Preliminary myofiber number in extensor digitorum longus muscle (n=3/group).

Role of insulin in fetal myoblast proliferation. Myoblasts isolated from IUGR fetuses and cultured *in vitro* demonstrate a *greater* propensity to proliferate in response to insulin in a dose-dependent manner compared to CON myoblasts under normoxic conditions, mediated by increased insulin receptor β (IRβ), a phenotype that persists after several passages in culture (Fig 7). This may seem paradoxical, but the proliferation potential of IUGR myoblasts *in vitro* in response to insulin indicates that insulin may have the potential to increase proliferation *in vivo* if given systemically. Indeed, we have shown that in CON fetuses during late gestation, a physiological increase in fetal insulin concentrations (from 0.3 to 1.0 ng/ml) with a concurrent euglycemic clamp increased the proportion of Pax7+ myonuclei by 20% (Fig 8b).

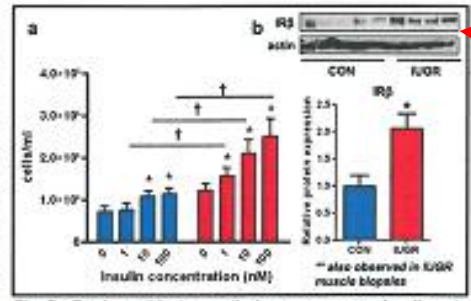


Fig 7. Fetal myoblast growth in response to insulin. a) Myoblasts harvested from IUGR fetuses (n=8, red) have a greater proliferative response to 5 day insulin exposure than do CON myoblasts (n=8, blue). *P<0.01 from 0nM; †P<0.05 CON vs. IUGR. b) Under basal conditions, insulin receptor β (IRβ) expression is increased in IUGR myoblasts.

Hypotheses: Given our preliminary data and a large literature base showing decreased numbers of myofibers in offspring that were undernourished as fetuses, we hypothesize that progressive reductions in circulating

Color is nice!

Need "significance" designations.

If you include blots, make sure they can be seen!

2. Muscle protein kinetics will be measured in the IUGR fetus. We will perform novel hindlimb catheterizations in the IUGR fetus to measure femoral arterial-venous concentration differences and blood flow (67) (Fig 4). A three-pool protein flux model and our unique multiple isotope infusion start time (MIST) method (3) will be used to measure muscle-specific protein synthesis, breakdown, and fractional synthetic rates, which has never been done before in the fetus.

Fig 4. Hindlimb surgery.

3. We will harvest muscle biopsies before and after experimental infusion in the same animal in which physiological measurements are made. Fetal muscle biopsies will be collected intra-operatively, which has never been done before in the fetus, and after experimental infusions to identify the effects of insulin and AA on myoblasts and myofibers. We have available cultured myoblasts (Fig 5a) and myotubes (Fig 5c) that retain *in vivo* characteristics (Fig 7&15) to determine the effects of insulin, AA, and oxygen independent of their complex interactions *in vivo*. We can localize protein expression within the proliferating Pax7+ myoblast (Fig 5d), including post-translationally modified cell cycle regulators (Fig 5e). A novel application of intact and viable muscle fibers will be employed to measure AA transporter activity (Fig 5f). *In vitro* studies on isolated fetal muscle add a new level of sophistication to classical whole animal fetal physiology studies. Our cadre of investigators with expertise in muscle biology make us the only laboratory that can perform these studies.

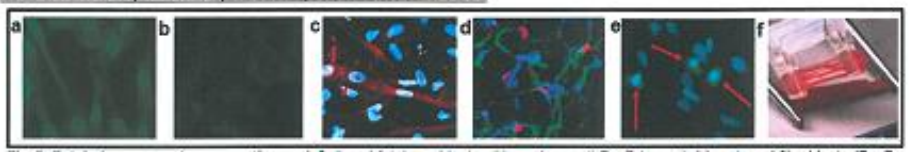


Fig 5. Fetal sheep muscle preparations. a) Cultured fetal myoblasts with nuclear anti-Pax7 (green); **b)** maternal fibroblasts (Pax7 negative); **c)** multinucleated myotubes with anti-desmin (red); **d)** cryosectioned muscle with anti-laminin (green), anti-Pax7 (pink), dapi (blue); **e)** myoblasts with anti-phosphorylated retinoblastoma (arrow); and **f)** intact muscle fibers held by a plastic clip.

C. Approach

As Elsie Widdowson, a pioneer of child nutrition and growth, stated in 1972 (68),

"if there is a cellular deficit resulting from malnutrition in utero this cannot be corrected postnatally."

This statement is supported by studies which show that muscle fiber number does not increase postnatally (62, 68-70). The fetal period is a critical time for the establishment of normal skeletal muscle mass. However, these studies were done over 30 years ago, and still the field suffers from an almost complete lack of understanding of how nutrient supply *in utero* regulates fetal muscle growth. Our proposal will answer fundamental questions about the mechanisms that produce fetal muscle growth restriction. Furthermore, we will challenge the paradigm that PI inevitably reduces muscle growth by targeting critical windows of fetal muscle development with anabolic stimuli. In Aim 1, we will determine the proliferative activity of fetal myoblasts and their response to restoring insulin concentrations. In Aim 2, we will determine the mechanisms by which myofiber hypertrophy fails and whether increasing AA supply improves myofiber growth. Finally, in Aim 3, we will correct both insulin and AA during appropriate developmental windows to test whether their combination is required to restore muscle mass in the IUGR fetus. Knowing the degree of plasticity and responsiveness of myogenesis after chronic PI will have a direct impact on how we ensure skeletal muscle growth early in the life span.

To accomplish our aims, we will use a highly relevant sheep model of chronic and progressive PI which results in decreased fetal nutrient supply and asymmetric fetal growth restriction. It replicates a natural condition of PI observed in sheep that is caused by increased ambient temperatures during pregnancy. This model has the same fundamental characteristics of human IUGR (Table 1) (71-78). The time course of myogenesis has been well described in fetal sheep (61). Thus, our large animal model is ideal to determine the regulation of muscle development under normal and pathological conditions, such as IUGR.

Table 1. Human and sheep placental insufficiency-induced IUGR

Placenta	Human	Sheep	*Fetus*	Human	Sheep
Weight	↓	↓	Weight	↓	↓
Uterine blood flow	↓	↓	BPD/abdominal circ ratio	↑	↑
Umbilical artery resistive indices	↑	↑	Arterial O_2 content	↓	↓
Umbilical blood flow	↓	↓	Plasma glucose	↓	↓
Transplacental leucine flux	↓	↓	Plasma insulin	↓	↓
Umbilical O_2 content	↓	↓	Plasma IGF-1	↓	↓
			Catecholamines	↑	↑

BPD, biparietal diameter

Color is nice!

Be sure you can see essential details in pictures.

Be sure all colors show up clearly.

Be cautions about too much underlining or bolding of text. Don't "over-emphasize".

If you include tables, make sure they can be read!

Include White Space

Follow the application guidelines

- Arial or Times New Roman 11 point font
- Single spaced, with 0.5’’ margins

Consider your reader

Do include white space between sections

- *Do* carefully use subheadings, indents, and bold/italics/underline
- *Don’t* feel obligated to fill the entire page limit – use only the space you need to tell your story

Grand Challenges Explorations
Bill & Melinda Gates Foundation

No silly mistakes

- All grant funding agencies are competitive!
  - *Do* proofread carefully and follow the guidelines for page limits, font sizes, etc.
  - *Don't* let silly mistakes hurt your chances
- Silly mistakes include
  - Typos
  - Exceeding page limits
  - Not defining abbreviations
- Not following instructions for formatting, content, structure, etc.

No silly mistakes

- Read the instructions before you start and again before you submit
- Finish your proposal before the deadline
  - Leave time for colleagues, co-PIs, or even your family to serve as peer reviewers and copy editors
  - Ask a native English speaker review your proposal
- Take a break and read your proposal fresh for final edits before submitting

Explicit Link to Funder

- Project needs to match funder's priorities
  - NIH or Foundation strategy
- Tips for providing explicit link to funder
  - Read RFA topic, foundation strategy, and instructions carefully
  - *Do* be specific about how your idea fits with strategy and RFA
  - *Do* be clear about how your deliverables contribute to solving the problem defined by the RFA

Tips from proposal reviewers:

- Tell a compelling story
  - Why? – define the problem and your unique solutions
  - What? – state a clear idea and experimental plan
  - What is the critical impact? – describe the path to scale
- Admit the risks
  - Define the level of high-risk, high-reward
  - Demonstrate your understanding of risks and plans to overcome
  - Define go/no-go experiments to thoroughly test proof of concept

Grand Challenges Explorations
Bill & Melinda Gates Foundation

And then your grant goes to

study section for review of its overall quality and scientific merit.

What Study Sections should do.

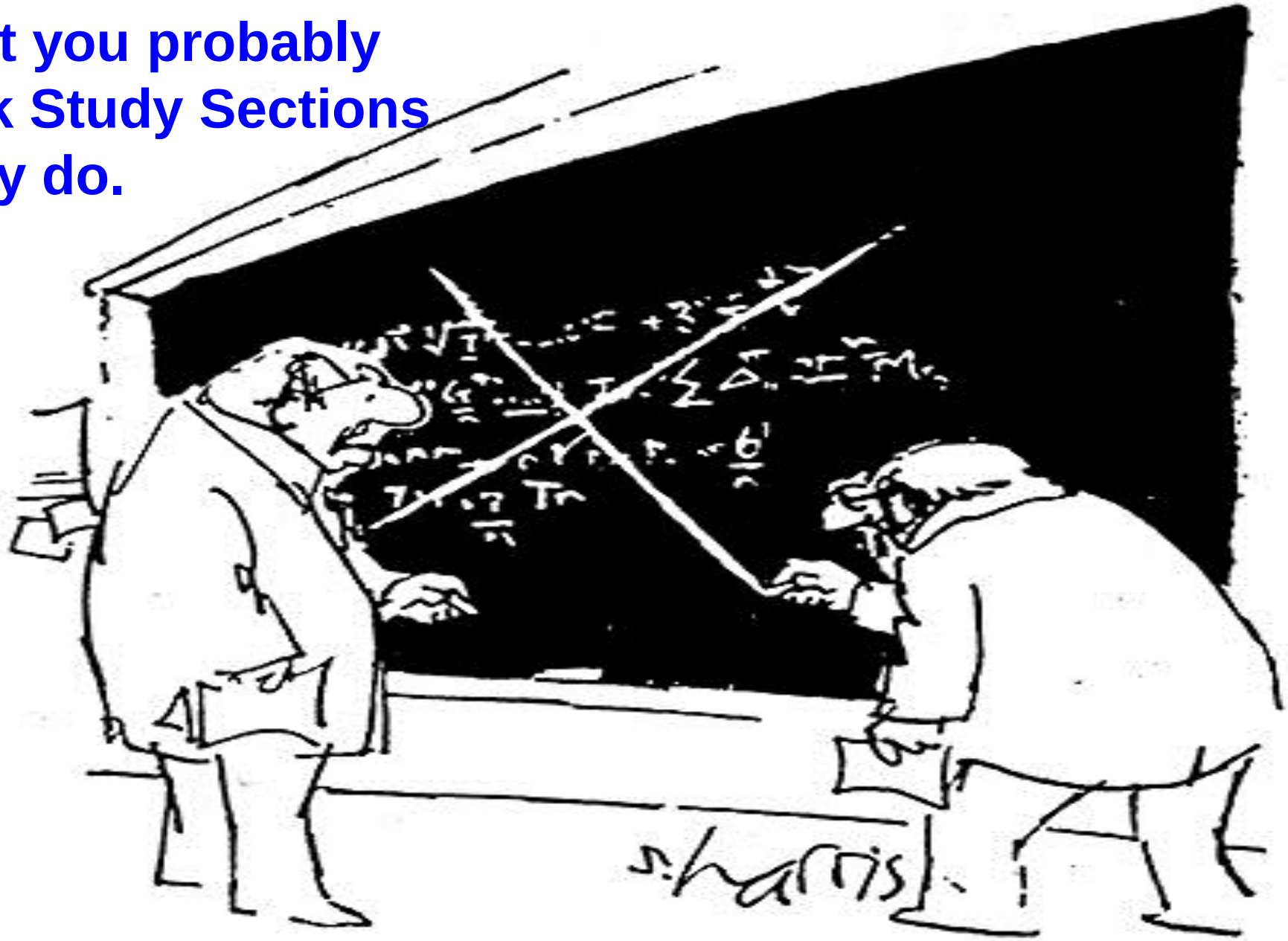
Study sections will give each application a single overall score to reflect "the study section's notion of what the likely impact of the proposal will be on our understanding of biology and behavior and on the practice of medicine."

Study sections are supposed to pay more attention to the potential impact of a grant application and less to its feasibility.

"Study Sections and NIH should be looking for the stuff that is truly distinguished."

Harold Varmus, J. NIH Research 9:31-32, 1997

What you probably think Study Sections really do.



"That's it? That's peer review?"

Score	Descriptor	Additional Guidance on Strengths / Weaknesses
1	Exceptional	Exceptionally strong with essentially no weaknesses
2	Outstanding	Extremely strong with negligible weaknesses
3	Excellent	Very strong with only some minor weaknesses
4	Very Good	Strong but with numerous minor weaknesses
5	Good	Strong but with at least one moderate weakness
6	Satisfactory	Some strengths but also some moderate weaknesses
7	Fair	Some strengths but at least one major weakness
8	Marginal	A few strengths and a few major weaknesses
9	Poor	Very few strengths and numerous major weaknesses

Minor Weakness: An easily addressable weakness that does not substantially lessen impact

Moderate Weakness: A weakness that lessens impact

Major Weakness: A weakness that severely limits impact

What happens?

Either —

Your grant scores well and gets funded,

Now get to work, and come back and tell the next group of young investigators how you did it.

Or—

Your grant is not so well scored and does not get funded.

What do you do now?

An understandable but inappropriate form of rebuttal.

Success

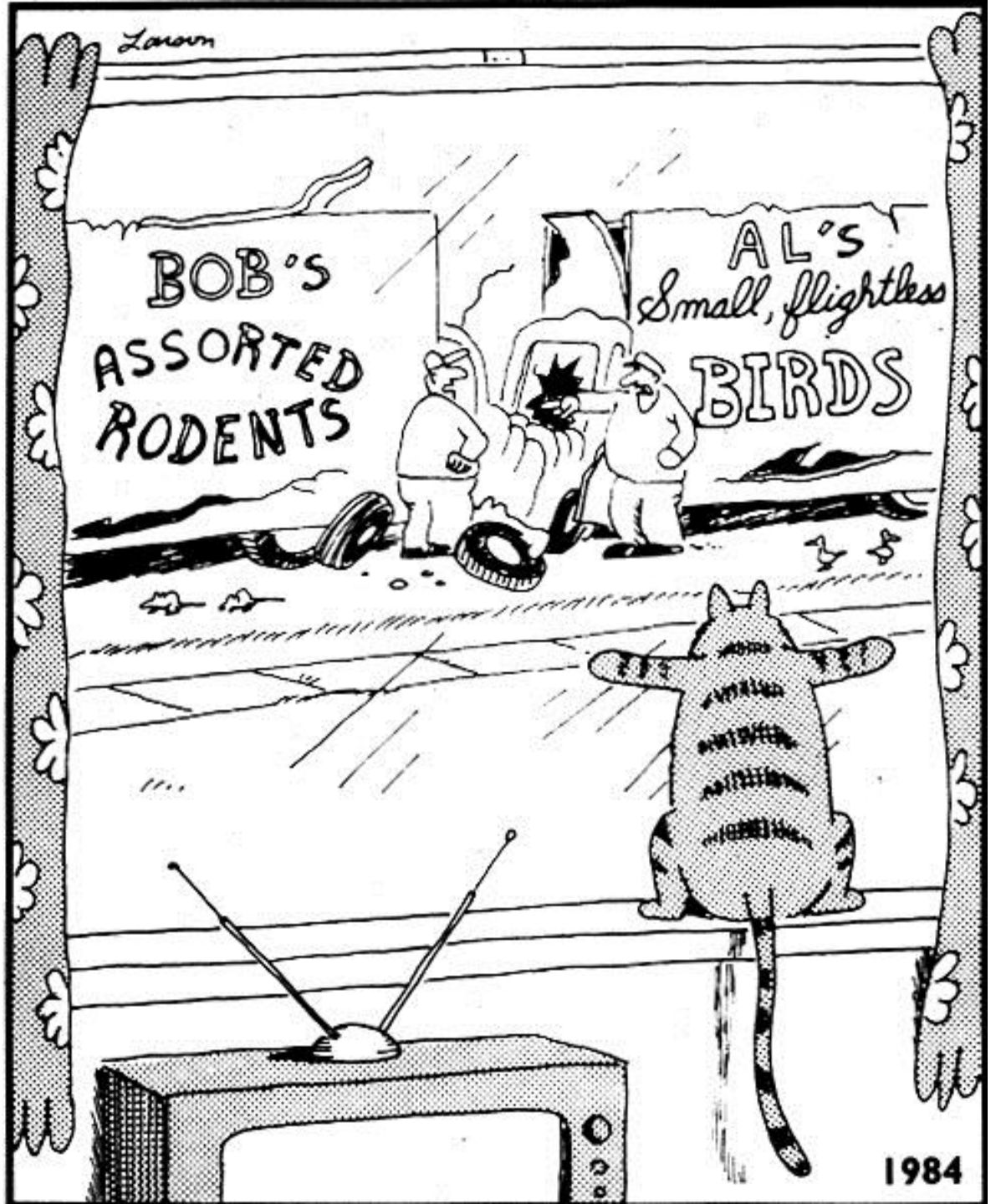
what people think
it looks like

Success

what it really
looks like

Resubmission

1. One page of introduction for response and/or rebuttal.
2. Address exactly each and every concern raised by the review.
3. But--focus response directed at the principal problems (you can use one response for the same critique from different reviewers).
4. Rebuttal should be well documented to support your position if you disagree with any point in the study section review.
5. Do not expand the grant unless directed to do so.
6. Keep the approved budget, but if you do change, make sure you tie the changes to a specific request of the study section.
7. No grant is perfect; use the revision opportunity to improve yours.
8. Above all, be polite.



If the reviewers want something different, give them what they want.

Critique Oriented Application

NIH now requires that your grant application specifically addresses each of the major review criteria—so—

- **Write your grant application to specially address the 5 major evaluation criteria used for the critique:**

  Significance, Innovation, Approach, Investigator, Environment,

  and include a Summary of these for the Abstract and at the end of the Text that emphasizes the overall Impact of the research.

- **Put the words you want the reviewer's critique to contain in your application.**

- **Document and justify every statement that relates to these evaluation criteria.**

Critique Oriented Application

- If an applicant has multiple Specific Aims, then the applicant may address Significance, Innovation and Approach for each Specific Aim individually, or

- may address Significance, Innovation and Approach for all of the Specific Aims collectively.

Many use a combination of both.

Critique Oriented Application

In the next section I will present

- **First:** NIH guidelines for what you need to put in your application
- ***Second:*** *what NIH asks the reviewers to learn from your application and write in their critiques*
- **Third:** what you should write in your application

1. Significance—NIH guidelines

- Explain the importance of the problem or critical barrier to progress in the field that the proposed project addresses.
- Explain how the proposed project will improve scientific knowledge, technical capability, and/or clinical practice in one or more broad fields.
- Describe how the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field will be changed if the proposed aims are achieved.

Critique Oriented Application

Significance—what the Reviewer should learn.

- Does the project address an important problem or a critical barrier to progress in the field?
- If the aims of the project are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved?
- How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

1. Significance

- **State how this study addresses, not just an important problem, but one that simply has to be resolved. Sell them!! about why this simply has to be done!**
- **State how, if the aims of the application are achieved, scientific knowledge will not "just" be advanced, but will be fundamental for any valuable future research.**
- **State how these studies and the results will drive the future of this field, using your novel concepts and/or methods to be the cutting edge.**

2. Innovation—NIH guidelines

- Explain how the application challenges and seeks to shift current research or clinical practice paradigms.
- Describe any novel theoretical concepts, approaches or methodologies, instrumentation or interventions to be developed or used, and any advantage over existing methodologies, instrumentation, or interventions.
- Explain any refinements, improvements, or new applications of theoretical concepts, approaches or methodologies, instrumentation, or interventions.

Critique Oriented Application

Innovation—what the Reviewer should learn.

- Does the application challenge and seek to shift current research or clinical practice paradigms by utilizing novel theoretical concepts, approaches or methodologies, instrumentation, or interventions?
- Are the concepts, approaches or methodologies, instrumentation, or interventions novel to one field of research or novel in a broad sense?
- Is a refinement, improvement, or new application of theoretical concepts, approaches or methodologies, instrumentation, or interventions proposed?

2. Innovation

- **State how the project employs novel concepts, approaches or methods.**

- **State how the aims are original and innovative.**

- **State how the project challenges existing paradigms or develops new methodologies or technologies.**

3. Approach—NIH guidelines

- Describe the overall strategy, methodology, and analyses to be used to accomplish the specific aims of the project.
- Include how the data will be collected, analyzed, and interpreted as well as any resource sharing plans as appropriate.
- Discuss potential problems, alternative strategies, and benchmarks for success anticipated to achieve the aims.
- If the project is in the early stages of development, describe any strategy to establish feasibility, and address the management of any high risk aspects of the proposed work.
- Point out any procedures, situations, or materials that may be hazardous to personnel and precautions to be exercised.

3. Approach—NIH guidelines

Preliminary Studies / Data for New Applications:

- Discuss preliminary studies, data, and or experience pertinent to this application.
- Preliminary data are an essential part of a research grant application and help to establish the likelihood of success of the proposed project.
- Early Stage Investigators should include preliminary data (for R01 applications, however, reviewers will be instructed to place less emphasis on the preliminary data in applications from Early Stage Investigators than on the preliminary data in applications from more established investigators).

Critique Oriented Application

Approach—what the Reviewer should learn.

- Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project?
- Are potential problems, alternative strategies, and benchmarks for success presented? If the project is in the early stages of development, will the strategy establish feasibility and will particularly risky aspects be managed?

- If the project involves human subjects and/or NIH-defined clinical research, are the plans to address 1) the protection of human subjects from research risks, and 2) inclusion (or exclusion) of individuals on the basis of sex/gender, race, and ethnicity, as well as the inclusion or exclusion of children, justified in terms of the scientific goals and research strategy proposed?

3. Approach

- **State how the conceptual framework, design, methods, and analyses are adequately developed, well integrated, and appropriate to the aims of the project.**
- **State/Acknowledge (with specific examples) potential problem areas and alternative tactics that you can reference to your lab(s) and/or the literature that will help resolve the problems. Convince the reviewer that you know this field inside and out, better than anyone else.**

4. Investigator(s)—NIH guidelines

This is what goes in your **Biosketch**

Provide your credentials

education, degrees, training, current position

Document your relevant experience and role in the proposal—your personal statement

Document your research to date

publications, grants

Define your co-investigators', collaborators', consultants'

specific expertise to conduct relevant parts of the experimental approachs.

Critique Oriented Application

Investigator(s)—what the Reviewer should learn.

- Are the PD/PIs, collaborators, and other researchers well suited to the project?
- If Early Stage Investigators or New Investigators, or in the early stages of independent careers, do they have appropriate experience and training?
- If established, have they demonstrated an ongoing record of accomplishments that have advanced their field(s)?
- If the project is collaborative or multi-PD/PI, do the investigators have complementary and integrated expertise; are their leadership approach, governance and organizational structure appropriate for the project?

4. Investigator

- **State (and document) how you--the investigator--are appropriately trained and well suited to carry out the proposed work.**
- **State how the proposed research is appropriate to your level of experience as principal investigator.**
- **State how other researchers will provide you with other essential aspects of the studies that you do not have yourself.**

5. Environment—NIH guidelines

Define what your institution provides for you—

- office, lab space, basic equipment and support personnel, commitment to provide the necessary time and effort for you to conduct the research.

Define unique features of your institution that will support specific aspects of <u>your</u> research.

- institutes, centers, programs, “technologies” in your area of science and how they provide support

Define animal and human subject support

- IRB/IACUC, animal facilities, human populations

Critique Oriented Application

Environment—what the Reviewer should learn.

- Will the scientific environment in which the work will be done contribute to the probability of success?
- Are the institutional support, equipment and other physical resources available to the investigators adequate for the project proposed?
- Will the project benefit from unique features of the scientific environment, subject populations, or collaborative arrangements?

5. Environment

- **State how the scientific environment in which the work will be done will contribute to the probability/guarantee of success.**
- **State how the proposed experiments will take advantage of unique features of your scientific environment or employ useful collaborative arrangements.**
- **Show evidence of institutional support. Letters of support must be specific, personal, and enthusiastic, and say how this work has to be done to advance the science of the field.**

Critique Oriented Application

Overall Impact

Reviewers will provide an overall impact/priority score to reflect their assessment of the likelihood for the project to exert a sustained, powerful influence on the research field(s) involved, in consideration of the scored review criteria, and additional review criteria as applicable for the project proposed.

Therefore, **you tell the reviewers** what the overall impact of your research will be and why it should have the highest priority.

6. Summary--Overall Impact

- **Summarize the important *strengths* of the application.**

- **Tell the reviewer *what you will learn* and *why this is essential and important.***

- **Tell the reviewer *how* the results of your proposed research—what you will learn—will produce a major impact on your scientific field and *how* the results will exert a *sustained, powerful influence* on the research field(s) involved.**

Preparing a Grant: COMMON MISTAKES

1. poorly written: bad grammar, typographical errors, poor outline, looks sloppy, too many words on a page, too much technical jargon

2. too much work proposed

3. not " crystal clear" what you want to do, why, and how

4. poorly justified; does not advance knowledge

5. necessary expertise is not demonstrated

6. too expensive

Preparing a Grant: COMMON SUCCESSES

1. The grant is easy to read
2. The science is "outstanding"
3. Written with evidence of confidence and enthusiasm for the importance and potential success of the proposed research
4. Figures, graphs, tables, charts, flow diagrams are self-explanatory as well as related to the text
5. The preliminary data/experience are organized to show how they will make the proposed experiments work successfully
6. The budget is accurately and thoroughly justified
7. Descriptive work is acknowledged as such; but the bulk of the research is testable hypotheses

OK, now go to the *grants.nih.gov* website and get started!

National Institutes of Health website

http://grants.nih.gov.html